REVIEW / Breast imaging

Dual-energy contrast-enhanced digital mammography in routine clinical practice in 2013

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KEYWORDS
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Abstract To date, analysis of the vascularisation of breast lesions mainly relies on MR imaging. However, the accessibility of MRI is sometimes limited and has led to the development of new means of imaging, such as dual-energy contrast-enhanced mammography, which provides data on the vascularisation of the breast along with the usual morphological information. The purpose of this paper is to present this new imaging technique as well as the recent references, illustrated by clinical reports derived from our everyday practice to focus on the advantages and disadvantages of this new breast exploration. Dual-energy contrast-enhanced mammography is a recent, seemingly promising technique, in the management of breast cancer. The main advantages consist of its easy installation, the good tolerance and the comfort in the interpretation of difficult to read mammograms. However, the indications and the role of dual-energy contrast-enhanced mammography still have to be determined within the diagnostic strategy of breast tumours. New studies are expected, especially to compare dual-energy contrast-enhanced mammography with breast MRI.

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Digital radiology has fostered the emergence of multiple innovations in breast exploration. Until now, MRI was the main technique used on a routine basis to study the enhancement of breast lesions. However, problems related to the accessibility of MRI may delay the care of patients with breast cancer.

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Contrast-enhanced mammography is an angiography technique using digital subtraction applied to the breasts. It was first mentioned in 1985 in the work by Watt et al. [1,2]. This imaging technique has been found to be interesting in erasing the normal mammary gland on subtracted images in order to frame breast tumours and visualise their vascularisation. The first machines have been marketed recently, following the clinical studies carried out at Institut Gustave-Roussy [3–6].

After a technical presentation and a review of the literature on contrast-enhanced digital mammography, this article will present different aspects of the dual-energy contrast-enhanced technique that may be encountered in clinical practice.

**Technical focus on contrast-enhanced mammography**

Contrast-enhanced mammography is based on the principle of digital subtraction between 2 images: one image containing information about breast vascularisation, the other about its morphology. The post-processing carried out on them reveals the ‘‘hyper-vascularised’’ regions of the mammary gland by freeing itself from its fibroglandular tissue.

**Temporal subtraction contrast-enhanced mammography**

The hyper-vascularised appearance of invasive malignant tumours was emphasised since the first work on contrast-enhanced mammography [7]. However, the distinction between benign and malignant tumours cannot be based on this aspect only. Like MRI, the temporal monitoring of the breast’s enhancement was studied to underline enhancement curve profiles (for example, a progressive enhancement profile is more often found with benign lesions [8,9]).

Therefore, the first method of contrast-enhanced mammography analysed a single specific incidence at different times after injection. The first image without injection of contrast agent was used as a mask. The opacified images were then digitally subtracted from the mask to produce the contrast-enhanced mammography images and only underlie the vascularised structures. According to the authors, 4 to 7 acquisitions were carried out each 60–120 s (Fig. 1) [8,10–12].

**Dual-energy contrast-enhanced mammography**

In 2003, Lewin et al. mentioned dual-energy contrast-enhanced mammography as an alternative to the temporal subtraction technique [13]. Based on the interaction between X-rays and iodine, it is possible to distinguish vascular structures, saturated by contrast agent, by a ‘‘high energy’’ image (beyond the attenuation coefficient of iodine, that is $K_{\text{iodine}} = 33.2$ keV) and the morphological information by a ‘‘low energy’’ image (below $K_{\text{iodine}}$). The digital subtraction of these 2 images only underlines the hyper-vascularised structures (Fig. 2a), as the temporal subtraction technique does.

**Value and validity of dual-energy contrast-enhanced mammography**

No clinical study could demonstrate a significant difference between the enhancement kinetics profiles observed for malignant and benign lesions. Therefore, contrast-enhanced digital mammography based on the temporal subtraction technique gave way to the advantages of the dual-energy technique [8,10]. While the temporal method limited the examination to only one breast and only one incidence, dual-energy contrast-enhanced mammography can be used to study and compare both breasts, in multiple incidences, with a better patient tolerance.

The main clinical study, carried out by Dromain et al., on 120 patients, compared dual-energy contrast-enhanced mammography with mammography alone or with mammography alongside ultrasound scan in the search for malignant lesions [4]. This work demonstrated a significant increase in sensitivity for dual-energy contrast-enhanced mammography (93%) when compared with mammography alone (78%), without a reduction in the specificity (assessed at 63%) [4]. In this study, dual-energy contrast-enhanced mammography did not provide an increase in diagnostic performance when compared with the mammography and ultrasound scan.

In view of these first encouraging results, the same team carried out a second clinical trial on the same population to assess the complementarity of dual-energy contrast-enhanced mammography with the mammography + ultrasound scan used in routine clinical practice [3]. This demonstrated an increase in diagnostic performance by the 6 readers (area under the curve significantly

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**Figure 1.** Principle of contrast-enhanced mammography using the temporal subtraction technique. According to the author, 4 to 7 acquisitions are obtained at a rhythm of one image every 60 to 120 s [8,10–12].
Dual-energy contrast-enhanced digital mammography

Figure 2. Principle of dual-energy contrast-enhanced mammography. a: formation of an image in dual-energy contrast-enhanced mammography according to the digital subtraction method. The post-treatment result reveals structures greatly absorbing high energy X-rays, like the vessels saturated with iodine contrast agent. It should be noted that the high energy images are not directly accessible on the consoles; b: dual-energy contrast-enhanced mammography protocol.

Practical focus on dual-energy contrast-enhanced mammography

Examination protocol

After installing the patient, 1.5mL/kg of contrast agent (Omnipaque® (iohexol) with an iodine concentration of 300mg/mL) are administered using an automatic intravenous injector if there are no contraindications. Two minutes after the injection, a medio-lateral oblique view and then a cranio-caudal view are obtained on the “non-pathological” breast. The “pathological” contra-lateral breast is then studied in the cranio-caudal and then medio-lateral images. There is a pause of one minute between images (Fig. 2b). The protocol may be stopped if the dual-energy contrast-enhanced mammography is “normal” (Fig. 3a). If there is an anomaly, the examination may be completed by a latero-medial and/or a spot compression view (Fig. 3b).
Main situations encountered in clinical practice

Locoregional metastasis

Breast cancers are intensely enhanced with hazy or spiculated contours in dual-energy contrast-enhanced mammography, as opposed to the rest of the mammary gland that is little or not at all enhanced (Fig. 4).

When breast cancer is clinically or radiologically suspected, dual-energy contrast-enhanced mammography may be useful to detect multiple homo- or contra-lateral cancers, with the injection of a contrast agent that helps reveal lesions that are not spontaneously visible by standard mammograms (Fig. 5) [5,6]. Dual-energy contrast-enhanced mammography also facilitates the ultrasound study of multiple lesions both to better detect them and also to more easily decide on those that require a biopsy.

In the main study by Dromain et al. assessing the efficiency of dual-energy contrast-enhanced mammography in breast cancer in 120 patients, the sensitivity is higher with dual-energy contrast-enhanced mammography (93%) than with mammography alone (78%) ($P<0.01$) without a loss of specificity (63% vs 58% with mammography, $P=0.64$) [4]. However, there is no significant difference concerning the sensitivity and specificity between dual-energy contrast-enhanced mammography and mammography plus breast ultrasound scan (90% sensitivity, $P=0.72$; 47% specificity, $P=0.08$).
Figure 4. A 65-year-old woman with invasive ductal carcinoma initially consulting for a right retroareolar breast mass with permeation nodules. On the right, images by dual-energy contrast-enhanced mammography with cranio-caudal (CC) view show an extensive right retroareolar enhancement opposite a clinical lesion and a suspect mass in the standard mammogram. The left breast is normal.

Compared with MRI that has a sensitivity between 89% and 96% according to the histological type, dual-energy contrast-enhanced mammography seems to provide the same range of results [15]. However, other studies are required in order to compare MRI and dual-energy contrast-enhanced mammography.

The case reported in Fig. 6 illustrates the difficulty in standard mammography in assessing correctly the position of the tumour compared with the nipple due to an architectural disorganisation whose limits are poorly visible, and the presence of a rounded retroareolar breast mass, while the contrast enhancement with dual-energy mammography helps better discern its extension. In this case, it also reassures us about the lack of enhancement of the rounded retroareolar mass that, after anatomopathological analysis, corresponds to a galactocele whereas the ultrasound scan might have seemed worrying due to the partially echogenic and irregular nature of the intra-cystic content.

Like with MRI, one of the current limits to locoregional metastasis search with dual-energy contrast-enhanced mammography is related to the discovery of non-visible lesions in mammography and ultrasound scan even after “second look” examinations (Fig. 7). In this young patient presenting a suspicious ACR5 mass in the right breast that is fully visible by mammography and whose limits are better distinguished on the subtraction image due to the enhancement of the cancer, a contra-lateral lesion was discovered.

Figure 5. Dual-energy contrast-enhanced mammography for a clinically detected nodule of the left axillary prolongation. Whereas the standard mammogram (top left) shows an architectural disorganisation in the left axillary prolongation (white arrow), dual-energy contrast-enhanced mammography (top right) reveals multiple enhancements and more easily allows for the detection of suspect images in ultrasound scan (at the bottom) and helps orient the biopsies.
A 61-year-old woman consulting for a left retroareolar breast mass. Whereas in the standard mammogram (on the left, medio-lateral oblique [MLO] view) several structures are superimposed, dual-energy contrast-enhanced mammography (centre) distinguishes the galactocele (white arrow) and invasive ductal carcinoma (black arrow), the only structure enhanced. The ultrasound scan (on the right) reveals a hypoechoic nodule (black arrow, invasive ductal carcinoma) and a mixed content cystic lesion (white arrow, galactocele). Without distinct translation in the mammography and ultrasound scan, dual-energy contrast-enhanced mammography then led to an MRI and then a biopsy under MRI to finally conclude to the discovery of a small fibroadenoma in the left breast. If biopsies were possible under dual-energy contrast-enhanced mammography, the patient would have been reassured more quickly and her treatment would not have been as complex.

Post-therapeutic monitoring
The scar tissue remodelling after breast surgery often appears as architectural distortions in standard mammograms. The distinction between post-therapeutic remodelling and cancer recurrence may prove to be difficult. The absence of enhancement in dual-energy contrast-enhanced mammography may increase confidence when confronted with images that are difficult to analyse (Fig. 8), in particular in dense breasts (Fig. 9), even if the usual radiology approach should not change according to the current state of knowledge. Dual-energy contrast-enhanced mammography may help distinguish non-vascularised, or little vascularised fibrotic tissue from a recurrence of breast cancer with an enhancement similar to that found in MRI.

Diagnostic assessment of abnormal imaging findings
After a classic breast examination (mammograms and ultrasound scan), probably benign lesions are often classified as ACR or BI-RADS 3, especially due to probable echogenic cysts. In this situation, dual-energy contrast-enhanced mammography, bilateral cranio-caudal view: suspect ACR5 mass containing microcalcifications in standard mammography with poorly defined limits. Discovery of nodular enhancement of the left breast corresponding to a fibroadenoma after macrobiopsy under MR imaging.
mammography may help distinguish between a purely liquid cyst (Fig. 10) and a cystic lesion containing a tissue portion (Fig. 11). Purely liquid lesions may directly be classified as benign ACR or BI-RADS 2 lesions without monitoring, and lesions with a solid component may be directly classified as ACR or BI-RADS 4 in view of a biopsy for a histological examination to determine whether or not there is an intra-canai or invasive component within the cyst.

Feedback

In the Centre d’imagerie de la femme at Hôpital d’Armentières, we assessed our practice during the first 6 months of use of dual-energy contrast-enhanced mammography (beginning in December 2011). Sixty-five patients benefited from dual-energy contrast-enhanced mammography. The mean age of the population was 53.8 years (37–77 years), 52% of them were menopausal.

Figure 8. Annual follow-up of a 55-year-old patient with a past history of right breast cancer, treated with a partial mastectomy in 2010. The clinical examination is normal. The standard mammogram (on the left) is not easy to read, especially due to asymmetric densities. The normal spot compressed images and dual-energy contrast-enhanced mammography reassured the patient.
Figure 9. A 68-year-old woman with a personal antecedent of right breast cancer treated by surgery. The standard mammogram (on the left) show dense, difficult to analyse breasts. The dual-energy contrast-enhanced mammography images do not reveal enhancement, which is reassuring. An ultrasound scan is carried out and is normal (no modification in the radiology procedure even though the dual-energy contrast-enhanced mammography is already reassuring).

Among the patients, 32% presented a family history of breast cancer and 31% personal antecedents of breast cancer.

Out of the 75 patients, 37 lesions were identified among 32 patients. Enhancement with dual-energy contrast-enhanced mammography was observed in 73% of the cases $(n = 27/37)$.

Among the 27 enhancements, 67% were malignant $(n = 18/27)$, including 13/18 corresponding to invasive ductal carcinoma (Table 1). Nine enhancements were benign $(33\%, n = 9/27)$, mainly corresponding to fibroadenomas $(n = 4/9)$.

Ten lesions were not enhanced, with a histology mainly related to fibroadenomas $(n = 7/10)$. The only false negative in this study corresponded to a lymphangitic carcinomatosis. This data was used to estimate the 95% sensitivity and the 85% specificity. The positive and negative predictive values were 67% and 98%, respectively.

The main artefact found in the series is matrix enhancement in 35% of the cases $(n = 26/75)$. It was pseudo-nodular for 58% $(n = 15/26)$ and diffuse for 42% $(n = 11/26)$ of them. The matrix enhancement hindered the interpretation of the enhancement in 4% of the examinations $(n = 3/26)$ since it was potentially masking.

Figure 10. Patient with dense multi-cystic breasts and attenuating zones that are difficult to interpret with standard mammograms (on the left) and ultrasound scan. Some cysts are ”atypical” (bottom right): echogenic cysts, with fluid level and doubt about a tissular portion, with thick walls, multi-loculated cysts. The exam is classified as ACR or BI-RADS 3 following the ultrasound scan. The dual-energy contrast-enhanced mammography (top right) does not reveal any intra-cystic enhancement. The exam may therefore be reclassified as ACR or BI-RADS 2. Dual-energy contrast-enhanced mammography reveals cysts in the form of ”phantom” images.
Limits of dual-energy contrast-enhanced mammography

False negatives in dual-energy contrast-enhanced mammography

Although dual-energy contrast-enhanced mammography is of interest in detecting hyper-vascularised lesions, little vascularised tumours may not be detected. In our series, we only observed one false negative, corresponding to lymphangitis carcinomatosis (Fig. 12).

Another cause for the non-visualisation of a lesion is the limited field as with mammography. Since the deep zones and axillary areas are difficult to explore, dual-energy contrast-enhanced mammography does not exempt from doing a full clinical examination and a complementary breast ultrasound scan in case of a strong clinical suspicion.

Moreover, the in situ study of carcinomas is poorly known. They may also be a source of false negatives in dual-energy contrast-enhanced mammography.

False positives in dual-energy contrast-enhanced mammography

Our series reported several cases of enhanced benign lesions (33%, n = 9/27). We observed 2 types of fibroadenoma enhancement: a slow profile, homogenising in late images, and a rapid profile, in early images (Fig. 13). This kinetics was also described in MRI [7,8]. A complementary ultrasound scan can correct the diagnosis if the characteristics are typical. In case of doubt, an ultrasound-guided biopsy may be carried out for a sure diagnosis.

Artefacts

The main artefact encountered is matrix enhancement. One hypothesis is that it results from extrinsic factors, such as the degree of compression of the breasts, and intrinsic factors, responsible for a diffused, non-uniform scattered radiation in the gland (Fig. 14a). Pseudo-nodular matrix enhancement (Fig. 14b) may be the cause of false positives due to the appearance that may seem to be suspect. In our series, a small number of examinations (n = 3) were potentially masked by matrix enhancement. In these cases, dual-energy contrast-enhanced mammography did not provide any additional information when compared to the mammography and ultrasound scan. Motion blur may also be observed in case of patient’s movement between

Table 1 Absolute and relative distribution of enhancement observed in 37 diagnosed lesions.

<table>
<thead>
<tr>
<th>Enhancement</th>
<th>Number</th>
<th>Proportion (%)</th>
</tr>
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<tbody>
<tr>
<td>Fibroadenoma</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Microcystic area</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lymphangitic carcinomatosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Enhancement of benign lesions</td>
<td>9</td>
<td>24%</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Microcystic area</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Papilloma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Angiomatosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intramammary lymph node</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Enhancement of malignant lesions</td>
<td>18*</td>
<td>49%</td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Intramammary lymph node</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* In 6 patients.
** Including 5 patients with multifocal cancer.
the high and low energy images (Fig. 14c). The radio-opaque structures seem displaced with a black edge. In case of motion blur, a cancer may be expressed by a “black carcinoma”: the enhancement of the cancer being masked by the movement artefacts (Fig. 14d). In this case, the diagnosis may be “corrected” on the other dual-energy contrast-enhanced mammography incidences like on the complementary mammography and ultrasound examination.

Glandular dose

The diagnostic reference level in digital mammography, as defined by Institut de Radioprotection et de Sûreté Nucléaire) (IRSN) in October 2011, is 1.8 mGy per image for a breast thickness of 45 mm under compression.

Out of the 104 patients benefitting from dual-energy contrast-enhanced mammography, 391 images were analysed (cranio-caudal and medio-lateral views): the mean thickness of the breast was 56 mm, the average mean glandular dose (MGD) was 2.65 mGy per image (including the low and high energy), for values ranging from 1.07 mGy to 4.76 mGy, and a standard deviation of 0.78 mGy (Table 2).

High energy acquisitions account for 25% of the total dose in dual-energy contrast-enhanced mammography with an average MGD of 0.65 mGy ([0.24—0.83], standard deviation of 0.23 mGy), vs 2.00 mGy ([0.84—3.74], standard deviation of 0.58 mGy) for low energy acquisitions.

The exposure of “standard” digital mammograms from the same patient population (360 cranio-caudal and medio-lateral views) was analysed: mean thickness of the breast of 57 mm, average mean glandular dose of 1.72 mGy per image ([0.74—7.82], standard deviation at 0.96 mGy).

The low energy acquisition, that provides a “classic” mammogram-like image, is 16% higher in our series than the standard digital mammograms in terms of exposure (2 mGy vs 1.72 mGy).

The total dose in dual-energy contrast-enhanced mammography is therefore 1.54 times higher than the dose in standard digital mammograms in our population at Centre Hospitalier d’Armentières.

Prospects for dual-energy contrast-enhanced mammography

From a technical point of view, one of the main disadvantages of dual-energy contrast-enhanced mammography is the current inability to carry out biopsies under dual-energy contrast-enhanced mammography due to the lack of a specific system of stereotaxy. Therefore, it is necessary to carry out breast MRI and then biopsies under MRI control, of enhancements visible in dual-energy contrast-enhanced mammography and not found in mammograms or during an ultrasound scan. This induces delays in the care and additional patient stress.

We had one case of discrepancy, detected with dual-energy contrast-enhanced mammography, between enhancement biopsied under MRI and a lesion initially seen in a mammogram (Fig. 15). It involved an error in the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Average mean glandular dose (MGD) measured in 391 dual-energy contrast-enhanced mammography images and 360 standard mammography images. The values are in milliGray.</th>
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<tbody>
<tr>
<td></td>
<td>MGD</td>
</tr>
<tr>
<td>Dual-energy contrast-enhanced mammography</td>
<td></td>
</tr>
<tr>
<td>High energy (HE)</td>
<td>0.65</td>
</tr>
<tr>
<td>Low energy (LE)</td>
<td>2.00</td>
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<tr>
<td>HE + LE (1)</td>
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<tr>
<td>Standard mammograms (2)</td>
<td>1.72</td>
</tr>
<tr>
<td>Ratio (1)/(2)</td>
<td>1.54</td>
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</tbody>
</table>
Figure 13. Dual-energy contrast-enhanced mammography image of a fibroadenoma. a: fibroadenoma with slow enhancement. The fibroadenoma (arrow) is better seen in the late dual-energy contrast-enhanced mammography image, 10 min after the injection; b: fibroadenoma with rapid enhancement (arrow). It should be noticed that the diffuse matrix enhancement prevents a good demarcation of the fibroadenoma that appears with blurred and irregular contours.
Figure 14. Artefacts in dual-energy contrast-enhanced mammography. a: diffuse matrix enhancement (black arrow); b: pseudo-nodular matrix enhancement (white arrow), associated with "phantom" images of cysts (black arrow); c: kinetic blur opposite surgical clips; d: the tumour that is enhanced after injection on the right side (black arrow), appears black and "not enhanced" in the medio-lateral oblique view due to the movement of the patient: black carcinoma (white arrow).

The value of dual-energy contrast-enhanced mammography when compared to MRI is to directly see the correspondence between the morphological anomalies detected in mammography on the low energy images and the enhancements visible in the recombined images. This advantage of dual-energy contrast-enhanced mammography over MRI did not avoid having the patient subjected to biopsies under MRI. If a system of sterotaxy under dual-energy contrast-enhanced mammography allowed for biopsy of the enhancement, it would also have been possible to biopsy the architectural distortion at the same time, under "classic" stereotaxy and thereby, reduce the care and patient anxiety. In the end, a benign angiomatosis lesion was found for the
enhancement and a sclerosing adenosis for the architectural distortion.

**Conclusion**

Dual-energy contrast-enhanced mammography is an interesting technique for the detection of tumoral lesions and provides diagnostic confidence when confronted with difficult to read mammograms. Its use as a complementary exam may be of particular use, in particular, in the assessment of the locoregional extension of breast cancer. This simple technique may be easier and quicker to access than MRI if dual-energy contrast-enhanced mammography spreads. However, additional studies are necessary to better specify the indications, diagnostic performance and its role in the strategy for the screening and care of breast cancer, in particular when compared to MRI.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


